Drug-related problems in hospitalised patients

A prospective bedside study of an issue needing particular attention

By

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Foreword

My interest in this area started when I undertook three months practical training in clinical pharmacy for the *specialist in hospital pharmacy* degree. After completing the degree there were no positions for clinical pharmacists in Norway, so I left hospital pharmacy and entered the field of drug utilisation. Finally, in 1998 the chief pharmacist called me back to start a small clinical pharmacy service at the medical department of Lovisenberg Diakonale hospital. I started with just a few hours per week on the ward and I really enjoyed it.

LOOK (Local Oslo group of clinical pharmacists) was started in 1998 by the four pioneers that held positions as clinical pharmacists in the Oslo hospitals. Throughout the years LOOK has been an important and supportive discussion forum for our clinical work. It was in this forum the first idea of a clinical pharmacy project was born.

I have always been fascinated by ice:
In early childhood – when I was sailing ice-floes in the Oslo fjord;
In young age – when seeking challenges at Svalbard and at the ice edge by the North Pole;
when skiing crosswise on glaciers and watching the glacier calve;
And now, being older and captured by the fascination of my profession,
I am excited of the iceberg as a metaphor.
Drug-related problems could be described as an iceberg. Adverse drug reactions – the ice above the water surface – being the overt problems felt by the patients. Underneath the surface – the main part of the iceberg – we find drug-related problems that might lead to disease and disaster.

Acknowledements

The data analysis and interpretation were performed at the Department of Pharmacotherapeutics, Faculty of Medicine, University of Oslo and at Lovisenberg Diakonale Hospital.

First of all, I would like to express my sincere gratitude to my supervisor, professor Åsmund Reikvam who has been very encouraging and helpful. When I worked on this project in addition to a full-time job, he inspired me to continue. Through these years, he has been a gentle and accessible supervisor. He dedicated time when I needed it, gave focused academic input to the research, spiritual vitality, but also resistance when I went in the wrong direction.

I also want to thank Tron Moger, my supervisor in statistics, for his valuable input and also his fast and constructive criticism.

The data collection was done by 7 dedicated clinical pharmacists, including myself. This group of pharmacists initiated the study and without them this work had never been completed. I will like to express my gratitude to Bodil Jahren Hjemaas, Frank Jørgensen, Piia Pretsch, Kirsten Viktil, Tine Flindt Vraalsen and Elspeth Walseth.

Also, I would like to thank the medical staff at the participating departments who during the study period contributed to a smooth, effective and friendly atmosphere in the multidisciplinary teams.

A special thank to Elspeth Walseth, co-author and colleague in clinical pharmacy for linguistic revisions.

I am very grateful that we were two clinical pharmacists continuing with the data analyses and interpretation. Kirsten Viktil has been on my side through thick and thin since we started the study. Like two musketeers we have struggled with the data, encouraged and supported each other. It has been a dedicated, fruitful, and always nice collaboration. I hope this collaboration may continue in the future and lead to new exciting research projects within the field of clinical pharmacy.

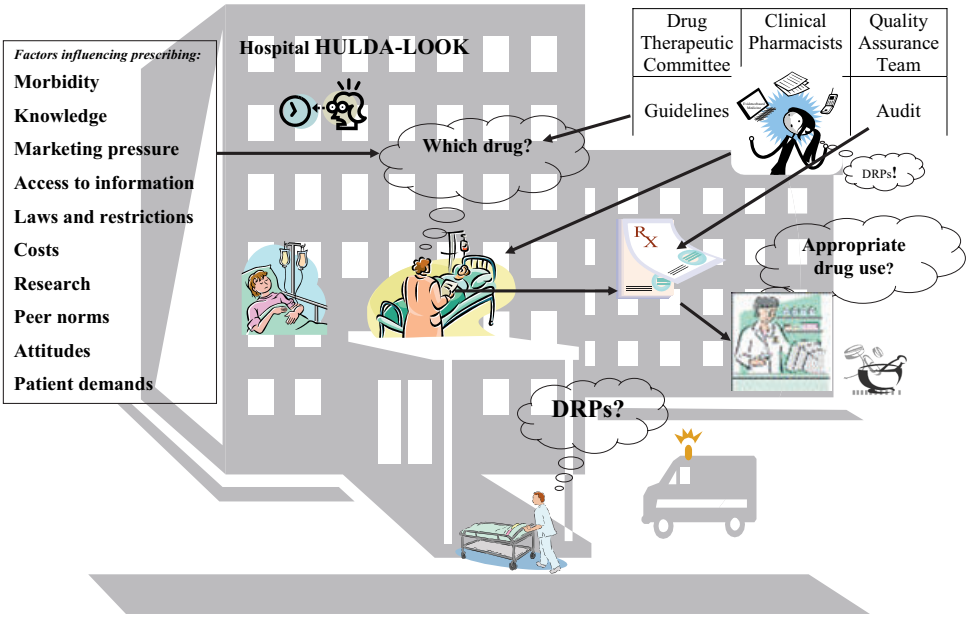
Thanks to Bjørn Holm, my contact supervisor at Lovisenberg Diakonale hospital.
Thanks to Eastern Norway Regional Health Authority (Helse Øst RHF), The Norwegian Community Pharmacy Foundation (Apotekfarmasifondet) and The Norwegian Pharmacy Associations' Foundation (Stiftelsen til fremme av Norsk Apotekfarmasi) for financial support.

I will also express my gratitude to two of my role models – Angelika Kruse-Jensen, who introduced me to clinical pharmacy and Kirsten Nordbø, my Chief pharmacist at Lovisenberg Hospital Pharmacy from 1987-1996, who always encouraged and inspired me. Thanks also to Marit Rønning, head of Department of Pharmacoepidemiology, Norwegian Institute of Public Health and Jan Egil Røe, Chief pharmacist at Lovisenberg Hospital Pharmacy, for giving me necessary leave of absence to complete this thesis.

Finally, a very special thanks to my family; my mother and father who gave me confidence and encouraged my curiosity; my husband Tormod and my children Vilde and Einar, who were there in daily life, making me remember that happiness is not the result of what you achieve, but rather the condition you feel on the way.

“Errare humane est”

Using drugs can be compared to using Damocles two-edged sword: there is a fine balance between good and evil – that is, between the wanted and the unwanted effects of a drug. The challenge is to find the optimal line where the effects are good and the unwanted effects are acceptable.



List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:

Paper I

Blix HS, Viktil KK, Reikvam Å, Moger TA, Hjemaas BJ, Pretsch P, Vraalsen TF, Walseth EK. The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals. Eur J Clin Pharmacol 2004;60(9):651-8.

Paper II

Blix HS, Viktil KK, Moger TA, Reikvam Å. Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. Pharm World Sci 2006;28(3):152-8.

Paper III

Blix HS, Viktil KK, Moger TA, Reikvam A. Use of renal risk drugs in hospitalized patients with impaired renal function – an underestimated problem? Nephrol Dial Transplant 2006;21(11):3164-71.

Paper IV

Blix HS, Viktil KK, Moger TA, Reikvam A. Comparison of two methods for identification of drug interactions: computerised screening versus bedside recording. Submitted.

These articles are part of a broader research project on DRPs. So far three other articles connected with the main project have been published:

Viktil KK, Blix HS, Reikvam A, Moger TA, Hjemaas BJ, Walseth EK, Vraalsen TF, Pretsch P, Jorgensen F. Comparison of Drug-Related Problems in Different Patient Groups. Ann Pharmacother 2004;38:942-8.

Viktil KK, Blix HS, Moger TA, Reikvam A. Interview of patients by pharmacists contributes significantly to the identification of drug-related problems (DRPs). Pharmacoepidemiol Drug Saf, 2006;15(9):667-674.

Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol, 2007;63(2):187-95.

Abbreviations, Definitions and Explanations

Abbreviations

ACE	Angiotensin-converting enzyme
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
DDI	Drug interactions
DRP	Drug-related problem
DRUID	The internet-based Norwegian Drug Information Database
GFR	Glomerular filtration rate
MDRD	Modification of Diet in Renal Disease
NSAID	Non-steroidal anti-inflammatory drug
RI	Renal impairment
SCr	Serum creatinine

Definitions and explanations

Adverse drug reaction (ADR)	Any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy (1). This definition excludes therapeutic failures, intentional and accidental poisoning, and drug abuse. The related term Adverse Drug Events (ADE) is an injury resulting from the use of a drug. This term also includes errors in administration.
Anatomical Therapeutic Chemical classification system	A drug classification system embraced by the WHO to be used in pharmacoepidemiological studies, administered by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway (2).
Clinical/pharmacological risk factor	Factors acknowledged to increase the risk of DRPs arising. In this work these are: polypharmacy, reduced renal function, reduced liver function, diabetes mellitus, cardiac failure, allergy, non-compliance, earlier reported ADR and other factors that may affect the patient's taking the drugs used.
Cockcroft-Gault equation	Estimated creatinine clearance (Cr.Cl.)(ml/min)= $\frac{(140-age) \times weight\ (in\ kg) \times constant}{SCr\ (in\ micromol/l)}$ Constant: 1.23 for men and 1.04 for women *Adjustments*: Cr.Cl. per 1.73 m^2 body surface: Cr.Cl. x 1.73/body surface. Body surface = 0,20247 x height (m) 0,725 x weight 0,425 (3).

Drug interaction (DDI)	An interaction is defined as occurring when the effects of one drug are changed by the presence of another drug, food, drink or some environmental chemical agent (4).
Drug-related problem (DRP)	An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (5). See also M-DRP and P-DRP.
Drug risk ratio	The number of DRPs associated with a drug (or a drug group) in relation to the number of times the drug (or drug group) is used.
Guidelines	Diagnosis-specific evidence-based drug recommendations developed by professionals.
MDRD formula	Estimated glomerular filtration rate (GFR)= **$32788 \times SCr\ (\text{in micromol/l})^{-1,154} \times \text{age (in year)}^{-0,203} \times \text{constant}$** Constant: 1 for white men, 0.742 for women and 1.21 for Africans; Absolute GFR = Estimated GFR x body surface/1.73m^2 Body surface = 0,20247 x height (m)0,725 x weight 0,425 (6).
Medication Error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of the health care professionals, patient or consumer (7).
M-DRP	DRPs may be counted in different ways. Medication-DRPs (M-DRP) are all countable DRPs connected to a drug.
P-DRP	DRPs may be counted in different ways. Patient-DRPs (P-DRP) are clinical DRPs as perceived by the patient.

Pharmacist advice	Any proposal made by a pharmacist for intervention with the intent of evaluating or changing the patient's drug therapy. Proposals relating to drug distribution, for example changing to a chosen generic brand, are not included in the definition.
Polypharmacy	The use of five or more different drugs (i.e. substances) concomitantly.
Rational drug use	Patients receive medication appropriate to their medical needs, in doses meeting their own individual requirements for an adequate period of time and at the lowest cost to them and the community (8).
Renal risk drugs	Drugs with recommendations for precautions in patients with reduced renal function.
Renoprotective drugs	Renal risk drugs that also have the property of protecting renal function.

1 Introduction

In the case of most diseases drug therapy will enhance health-related quality of life. However, inappropriate use of drugs may be harmful and could evoke new adverse symptoms. This has been known for centuries but, it was first when the reports of aplastic anaemia following treatment with chloramphenicol (9) and of birth defects after use of thalidomide (10) that the interest in drug-related problems (DRPs) increased dramatically. Since then, research in this field has been intensified, as has the development of more effective and targeted drugs, and the pharmaceutical industry has grown into one of the most important industries in the world. A paradoxical consequence is that drug therapy has gradually become more complex, thus making it increasingly challenging to prescribe drugs appropriately.

1.1 To set the scene

The headline in Pharmacy Today, 2001 "Drug-related problems: Once a $ 76.6 Billion headache, now a $ 177.4 Billion migraine" (11) not only underlines the societal consequences in terms of costs but also illustrates the chronic impact of DRPs on morbidity and mortality (12). DRPs are of major concern in view of their physical, psychological and economic burden to the patients and to society as a whole (13;14). Thus, optimising drug therapy – by preventing drug-related problems – may influence the health costs, potentially save lives and enhance patients' quality of life (15-17).

Previous studies have mainly addressed DRPs as a cause of hospitalisation (18-25). However, DRPs that arise in the hospital setting – under treatment – have rarely been described.

Several administrative initiatives concerning drug quality have been implemented with the aim of achieving rational prescribing in hospitals. However, tools like guidelines, printed educational material, drug surveillance, audits on drug handling and retrospective feedback to prescribers have been reported to have only limited effects (26-28). Moreover, the fact that daily life in a hospital, characterised by high patient turnover, lack of time, high speed and unplanned events – in many ways a chaotic situation – gives limited room to evaluate existing long-term drug treatment. In addition, when treatment with a new drug is started it is difficult, owing to the short hospital stay, to optimise the dosage. Also, since steady state often has not been reached, it is hard to evaluate the long-term effect and the outcome of possible interactions of the new drug with already established drug regimens. This makes it necessary to heighten the focus on drug use in hospitals. Preferably, an interdisciplinary approach should be put in place to ensure decisions that result in an optimal and rational drug therapy for the individual patient, which would reduce the frequency of avoidable drug-related problems and benefit society as a whole.

1.2 What are drug-related problems (DRPs)?

Adverse drug reactions (ADRs) have been the problems most frequently investigated. However, the practical focus in the field of rational pharmacotherapy is much broader than just dealing with ADRs. In the long run, other DRPs, such as drug use without an indication, improper drug selection, improper dosages, absence of necessary drugs, may be as important as ADRs.

This illustrates the need for a broad approach to the issue of DRPs. By identifying all types of problems, also potential DRPs, precautions may be taken to prevent these from

becoming overt clinical problems. Furthermore, a broad definition of what constitutes a DRP could provide a basis for understanding the whole spectrum of these problems.

1.3 How may DRPs be identified?

DRPs have often been addressed by studying large databases (29-31). However, the clinical approach – bedside evaluation – increases the likelihood of identifying true DRPs, whereas database studies may find "artificial" DRPs, e.g. they may identify as inappropriate a drug that in fact is appropriate for the patient in question.

Identification of DRPs demands tools. Explicit criteria such as guidelines and lists of drugs with rules of caution are important in this respect but have been somewhat controversial because they do not identify all cases of potentially inappropriate prescribing (32-34). Implicit review is necessary in the clinical evaluation of individual therapy. On the other hand this method, if used alone, could introduce biases connected to the reviewer (e.g. opinions and knowledge) that are difficult to identify.

In this study we decided to undertake an implicit review by investigating how DRPs were dealt with by multidisciplinary hospitals teams with a clinical pharmacist on board. We also decided to use two explicit National lists prepared by specialists in the field, one being the recommendations for drug management in patients with reduced renal function and the other the list of drug interactions (DDIs).

1.4 Clinical pharmacists

Clinical pharmacy is defined as a health speciality, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of

medicinal products and devices (35). Within this definition we find different categories of practice ranging from patient education to pharmacokinetic services to participation in rounding teams, the last being sometimes described as collaborative drug therapy. Clinical pharmacists can play a vital role by addressing the whole range of drug therapy in hospitals and, in general, the clinical pharmacy services have been reported to improve patient care by reducing inappropriate prescribing (36;37), improve disease management (38;39), diminish adverse drug events (40), reduce length of stay, ADRs and mortality (41) and give economic benefit (42). More specifically, involving the clinical pharmacy service in collaborative drug therapy, that is to say, direct and prospective cooperation between physicians and pharmacists on an individual patient's drug therapy, has been increasingly acknowledged. This collaborative process is designed to optimise the patient's drug therapy and health-related quality of life. This type of clinical pharmacy service (rounding team) has been shown to improve clinical outcome (43) and reduce adverse drug events in hospitals (44;45). The collaboration between pharmacists and physicians has been welcomed by the World Medical Association who stated (1999) "physicians and pharmacists have complementary and supportive responsibilities in achieving the goal of providing optimal medicinal therapy. This requires communication, respect, trust and mutual recognition of each other's professional competence" (46).

Clinical pharmacy services have evolved differently in the various countries, influenced by differences in clinical settings, national therapeutic traditions, culture and the structure of the health care systems. In Norway, clinical pharmacists in hospitals have taken a proactive approach, cooperating directly with physicians and other health professionals in multidisciplinary rounding teams (collaborative drug therapy) and are also in direct contact with patients. In studies evaluating the pharmacist's contribution, exact details about the type of clinical service are sometimes lacking. Thus, the impact of the pharmacy service is

sometimes difficult to assess, since the outcome is dependent on which pharmacist approach has been applied. In this study we have applied the current model used in Norwegian hospitals, implying that our results will reflect a multidisciplinary proactive approach.

1.5 Drugs used in patients with renal impairment

Many patients admitted to hospital have reduced renal function (47-49). However, the spectrum of chronic kidney disease extends from slight kidney impairment to severe renal damage. In most patients with mild to moderate renal impairment the reduced function may not have been diagnosed and these patients are managed in general practice and in general hospitals.

Many drugs and their metabolites are eliminated through the kidney. Inappropriate use of drugs in patients with renal impairment may cause harm, which makes the handling of these patients particularly challenging. Guidance on drug management in patients with reduced renal function has therefore been considered to be important, and explicit lists with recommendations are available in most countries (50;51). These lists have been developed by specialists in the field. They give general recommendations, are adapted to the national drug market and are updated routinely. These guidelines are of little value, however, if a deteriorating renal function is not acknowledged. Furthermore, we do not know to what extent these lists are used in clinical practice.

1.6 Drug interactions

The impact of drug interactions (DDIs) has been known for a long time. However, it is only during the recent decades that crucial mechanisms causing interactions have been delineated

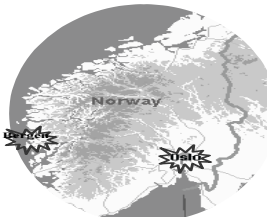
and fully understood. This new knowledge has escalated the recognition of a huge number of drug interactions, making it almost impossible for the individual prescriber to keep updated and to remember all potentially hazardous drug combinations. Explicit lists of DDIs developed and updated by specialists in the field are available in most countries (50;52). Moreover, sophisticated computer programmes based on the lists are available for screening of the patients' medication profiles. However, screening takes time and, furthermore, provides only a rough estimate, since an identified DDI might be of minor clinical importance in one patient but extremely serious in another. Most clinicians agree that it is important to be aware of problematic DDIs associated with a patient's drug regime, but it has not been settled which method is most efficient for the identification of clinically important DDIs.

2 Aims of the study

The purpose of this study was to investigate the occurrence and management of drug-related problems (DRPs) in a hospital setting. The specific aims were as follows:

- to identify and describe the magnitude and types of DRPs in hospitalised patients (Paper I)
- to identify risk factors for DRPs and the drugs that most frequently cause DRPs (Paper I)
- to investigate the extent to which pharmacists contribute to the therapeutic hospital team in terms of evaluating the drug regimens of individual patients (Paper II)
- to investigate the pharmacists' priorities on drug issues, their therapeutic advice and how this advice is dealt with (Paper II)
- to investigate the appropriateness of drug use and the occurrence of DRPs in hospitalised patients with mild to severe renal impairment (Paper III)
- to evaluate and compare two methods – computerised screening and clinical bedside recording – as regards the capability to identify drug interactions in hospitalised patients (Paper IV)

3 Materials and methods



3.1 Study design

The four papers included in this thesis are based on a multicentre investigation. The study was designed primarily to investigate the occurrence of drug-related problems (DRPs) in general hospital populations, but also to examine interventions in relation to the observed DRPs. Thus the study can be described as both a clinical study and a prospective observational cohort study.

3.2 Study population

The clinical data were collected at five hospitals during the period May to December 2002. Four of the hospitals are located in Oslo, the capital of Norway and its largest city (approximately 550 000 inhabitants), and one in Bergen, the second largest city in Norway (approximately 235 000 inhabitants). Wards that had specifically appointed clinical pharmacists to rounding teams were selected for participation. The pharmacists (i.e. the data collectors) visited the wards three to five days per week (one ward two days a week), weekends not included. Since most of the patients admitted during a weekend were hospitalised for a longer time than just the weekend, nearly all the hospitalised patients were captured and recruited to the study.

Patients admitted to six wards for internal medicine – represented by cardiac, respiratory and geriatric wards – and two wards for rheumatology were enrolled in the study **(Figure 3.1 and 3.2)**. Emergency departments were not included. All of the internal medicine

wards were acute general wards with patients admitted from local general practices. The rheumatology departments had regional referral. Patients were included in the study consecutively and followed up prospectively during their hospital stay. Patients who were readmitted during the study period were included on first admission only.

Figure 3.1 *Patient enrolment to the various wards at the various hospitals. Hospitals included were: Haukeland University hospital (H), Ullevål University hospital (U), Lovisenberg Diakonale hospital (L) Diakonhjemmets hospital (D), Aker University hospital (A).*

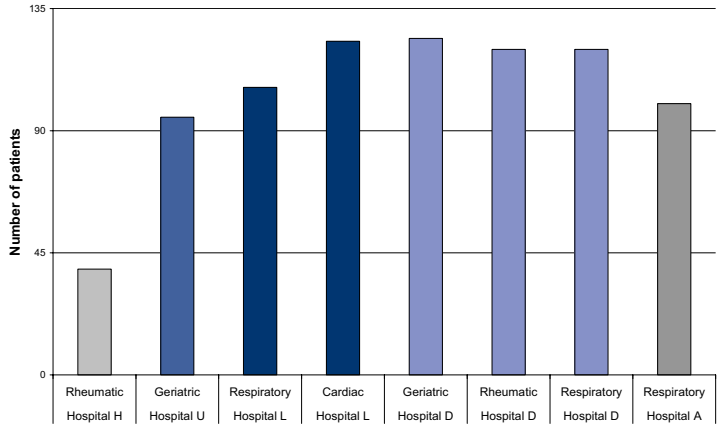
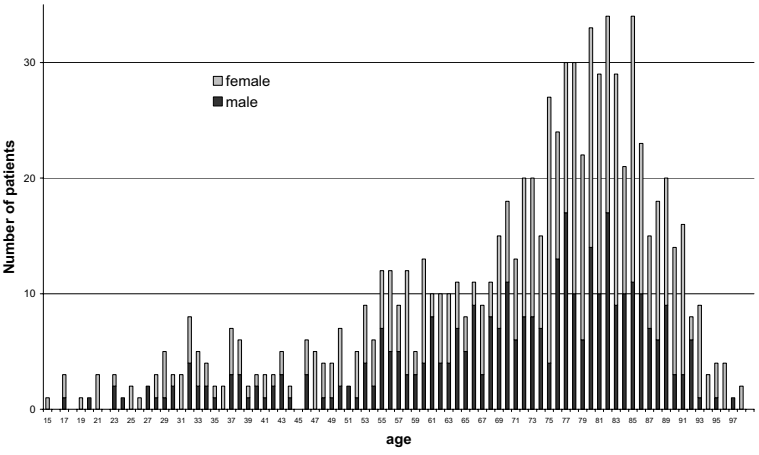


Figure 3.2 *Patient distribution by age and gender.*

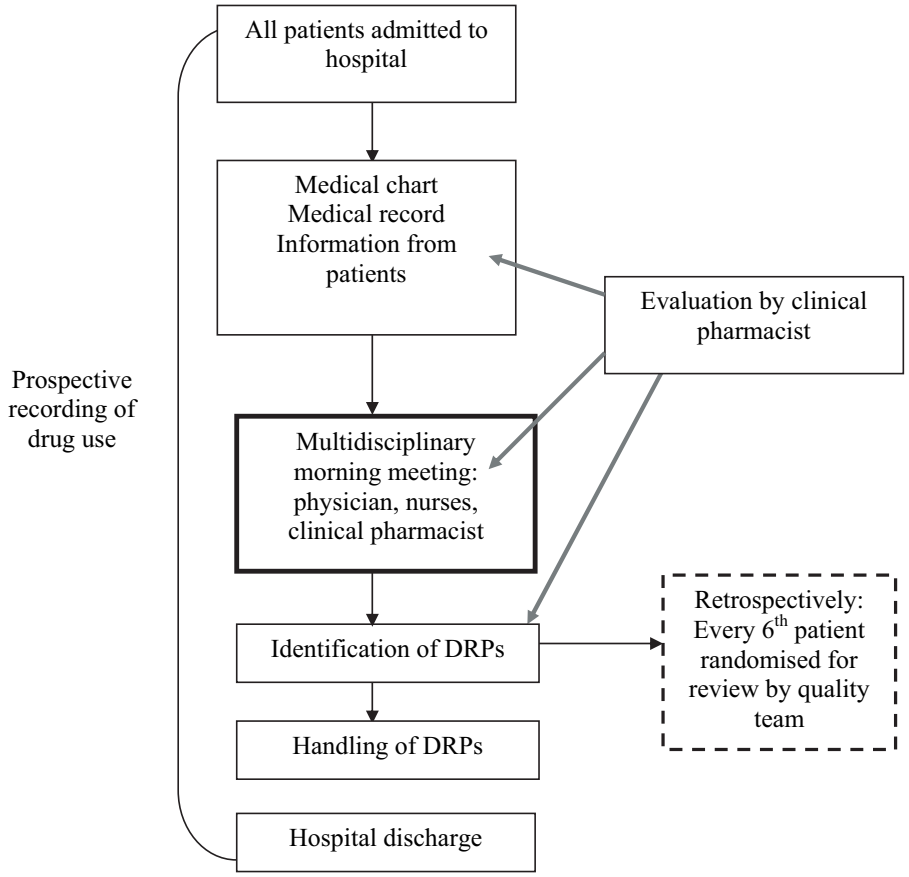


3.3 Data collection

The patients were approached individually. Experienced clinical pharmacists collected data from medical charts, medical records, physicians' ward rounds and the multidisciplinary meetings where each patient was discussed with regard to diagnosis, management and follow-up **(Figure 3.3)**. Participants at the morning meeting were physicians, nurses and clinical pharmacists, and occasionally physiotherapists and other health professionals. Information was also collected, if possible, by talking with the patients. A standard data recording form was used **(Annex I)**. The form had been designed, tested and found applicable to the participating departments.

The following data were recorded for each patient: age, gender, drugs used at admission, drugs started during the hospital stay, relevant medical history, reason for hospitalisation and results of routine laboratory tests. Some specific factors that are assumed to increase the risk of DRPs arising were recorded. The selected factors were those most often mentioned in the literature as risk factors. These, which are a mixture of pharmacological, clinical and patient-related factors, here called clinical/pharmacological risk factors, were the following: polypharmacy (defined as ≥5 drugs at admission), reduced renal function (glomerular filtration rate (GFR) below 50 ml/min or serum creatinine (SCr) above normal range), reduced liver function (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) three times above normal values), confirmed diabetes mellitus, cardiac failure, history of allergy or adverse reactions to drugs, assumed non-compliance (based on information gathered from the patient, medical record or health care staff), use of drugs with a narrow therapeutic index (defined by an explicit list in the data collection form), and other factors that could affect taking the prescribed drugs, including alcohol misuse and swallowing problems that might hamper intake of the drugs in question.

Figure 3.3 *Flow chart for the prospective multicentre study.*



3.4 DRPs

Drug-related problems (DRPs) were defined in accordance with the definition of Pharmaceutical Care Network Europe: "*a drug-related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"* (5). Operational classification of DRPs was performed according to a modified version of Strand et al (53) (**Table 3.1)**. At the time of data collection this classification had already been used for some years in daily routine by a network of Norwegian hospital pharmacists (Local

Oslo Group of Clinical Pharmacists, LOOK) in an attempt to standardise the classification procedure. The clinical pharmacists participating in this study as data collectors were part of that network. Consequently, the participating pharmacists had a common understanding of the classification used in the study.

The pharmacist assessed whether the patient had DRPs by using explicit criteria listed in national (50) and local guidelines and Felleskatalogen (The Norwegian Drug Catalogue) (52). The guidelines include separate lists of drug interactions as well as separate lists of drugs that are inappropriate to use in patients with renal or liver failure. DRPs that had been identified and handled appropriately were no longer a problem and consequently were not recorded as such. Some DRPs (a minor proportion) were identified by the pharmacist, and although not discussed or acted upon were nevertheless recorded as DRPs. Most DRPs were evaluated by the multidisciplinary team which was chaired by the physician, who made the final decision about acknowledgement of DRPs and what action should be taken.

One specific drug may introduce more than one DRP, some of them being interdependent. For example, a given drug may have caused an interaction, leading to too high dosage and a need to monitor the effect of the drug by means of laboratory tests. Thus, three DRPs could be related to the drug, but the patient might perceive only one DRP – the actual drug itself. Therefore the frequency of DRPs per patient was specified both as the number of Medication-DRPs (M-DRP), a term primarily suited for scientific purposes, and as the number of Patient-related DRPs (P-DRP). Consequently, the number of M-DRPs is higher than the number of P-DRPs. In Paper I both ways of classifying DRPs were applied. In Papers II, III and IV, the first approach was used and the reported frequencies of DRPs were based on the counting of all recorded DRPs.

We also introduced a "*drug risk ratio*" for each drug, which was the number of DRPs in relation to the number of times the medication was used.

Table 3.1 *Classification of drug-related problems (DRPs).*

• Need for additional drug
• Unnecessary drug
• Non-optimal drug, incl. non-optimal drug formulation
• Non-optimal dosing, incl. non-optimal dosing schedule
• No further need for the drug
• Drug interactions
• Need for monitoring
• Adverse reaction (experienced)
• Medical chart error
• Patient education required
• Specific information/discussion of therapy
• Patient adherence problems
• Others

3.5 Pharmacist interventions (i.e. pharmacist proposals for therapy interventions)

The pharmacists participated in the meetings of the multidisciplinary therapeutic team. In these team meetings the identified DRPs were brought up for discussion and evaluation (**Figure 3.4**). The pharmacist's advice was recorded, along with the physician's decisions regarding the patient's drug therapy. Pharmacist advice was defined as: *"any pharmacist proposal for intervention made with the intent to evaluate or change the patient drug therapy"*. Proposals concerning drug dispensing and distribution, aimed at assuring compliance with drug therapy lists, were not included.

Responses to the pharmacist's advice were recorded in three categories:

1. "Yes" - immediate acceptance by the physician and subsequent action.
2. "No" - the physician did not approve the pharmacist's proposal and no action was taken.
3. "Accepted" - agreed by the physician, who noted the proposal, but no immediate action was taken.

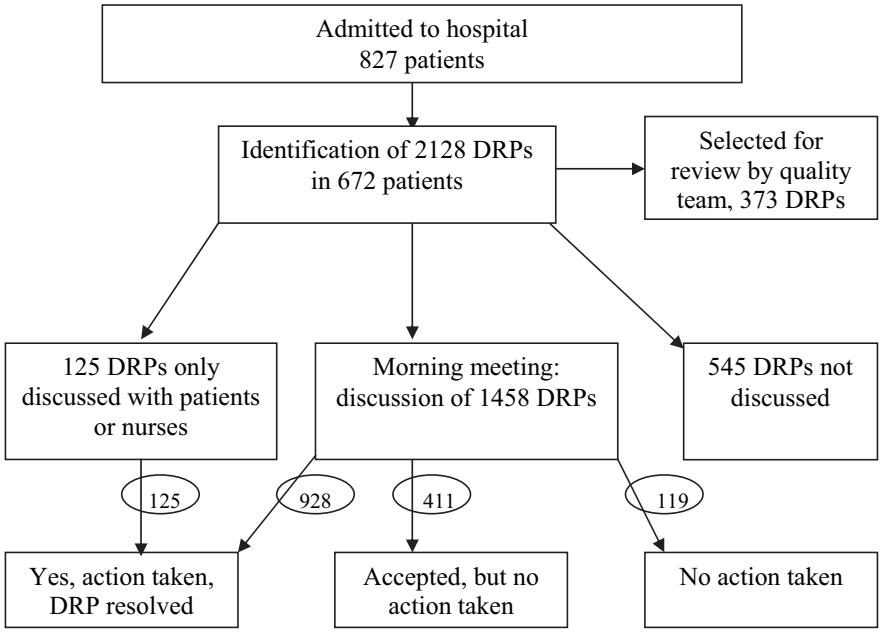
Some DRPs connected with proper drug handling were not brought up for discussion with the physicians, but were discussed directly with the nurses handling the drugs at the hospital or with the patients themselves. These DRPs were recorded separately as pharmacist advice to nurse/patient.

Some pharmacist-identified DRPs were not brought up for discussion, either with physician, nurse or patient. In such cases the reasons for not discussing an identified DRP were noted, and were grouped as follows:

1. "Not given priority" - e.g. DRPs that could not appropriately be solved at the hospital or in the specific clinical situation, or that other DRPs were considered by the pharmacists to have higher priority.
2. "No longer relevant" - e.g. the DRPs were solved before the team discussions took place, or the patient had died or been transferred to another department/hospital.
3. "Other reasons" - e.g. the DRPs were not given immediate priority at the time, but the intention was to discuss them later during the hospital stay.

The patients with DRPs were grouped into three categories: patients all of whose DRPs were discussed; patients some of whose DRPs were discussed; patients none of whose DRPs was discussed.

Figure 3.4 *Flow chart showing how pharmacist-identified DRPs were handled.*



3.6 Grading of renal impairment and renal risk drugs

The patients were divided into groups according to grade of renal impairment (RI). The grading into five stages of RI was made in harmonisation with the definition given by the National Kidney Foundation (54) (**Table 3.2**). This grading is based on the GFR. The Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends that GFR be calculated from calibrated SCr and estimating equations. Two main methods are recommended: the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) formula.

Table 3.2 *Renal function classified according to the National Kidney Foundation's definition (54).*

stage 1 (normal kidney function)	GFR ≥ 90 ml/min/1.73m^2
stage 2 (mild reduction of GFR)	GFR 60-89 ml/min/1.73m^2
stage 3 (moderate reduction of GFR)	GFR 30-59 ml/min/1.73m^2
stage 4 (severe reduction of GFR)	GFR 15-29 ml/min/1.73m^2
stage 5 (kidney failure)	GFR ≤ 15 ml/min/1.73m^2

Until recently, the Cockroft-Gault equation has been the reigning method of calculating GFR in Norway and the MDRD method was not used widely in clinical practice until 2006 (55). The Cockcroft-Gault equation is considered to be a good bedside estimate of renal status when considering drug therapy. Therefore, together with the usual pragmatic clinical evaluation of the level of SCr as a marker of renal function, the Cockcroft-Gault equation was used prospectively during the study period to find out into which category of renal function the patients should be registered. Patients with reduced renal function were regarded to be at risk for occurrence of DRPs (see 3.3 data collection, clinical/pharmacological risk factors).

The Cockcroft-Gault method calculates creatinine clearance based on age, gender, SCr and patient's weight. Information about weight was not available for all patients. The MDRD formula is simpler, since it requires only information on SCr, gender and age. Retrospectively we applied this simpler formula to calculate the GFR for nearly all the patients included in the study (808 of 827 patients). SCr was not obtained for 19 of the patients. We used the National Kidney Foundation's GFR calculator to calculate GFR by means of the MDRD formula (56). Patients in stages 1 and 2 (normal or mild reduction of renal function) were considered to have adequate kidney function in relation to drug therapy, while patients in stages 3, 4 and 5

were considered to have impaired renal function and to be in need of special attention as regards drug therapy.

Precautions are recommended when certain drugs and classes of drugs that are eliminated through renal excretion are to be used in patients with RI. These drugs were designated renal risk drugs. We used the lists and recommendations in the Norwegian National Therapy Guidelines (50) and similar lists in the British National Formulary (51) to assign drugs to the renal risk drug group. Further, we classified renal risk drugs into three main categories: *drugs for which dose adjustments are recommended*; *drugs to be used with caution*; *drugs to be avoided* in patients with RI (**Table 3.3)**. Some renal risk drugs were classified into more than one category, for example, in the cases of the benzodiazepines, caution is advised owing to cerebral sensitivity in patients with RI, and it is recommended that in patients with this condition the therapy should be started in small doses, i.e. the dose should be adjusted.

Some drugs included in the lists of renal risk drugs may also have renoprotective properties. These – with recommendations for handling in the event of RI – are: ACE inhibitors (caution – reduce dose); angiotensin II antagonists (caution – reduce dose); calcium channel blockers (caution when initiating therapy); some statins (simvastatin: dose above 10 mg to be used with caution, pravastatin: start with small doses, fluvastatin: avoid in severe RI). These drugs were included in the total number of renal risk drugs, but were also depicted separately as renoprotective drugs.

In order to better describe the risk to the individual patient we introduced the "*proportion of drugs at risk*", i.e. the proportion of renal risk drugs in relation to the total number of drugs used.

Table 3.3 *Categorisation of renal risk drugs and drug groups with special recommendations for use in patients with renal impairment (RI).*

	Drug groups (ATC) with general cautions rules in RI
Dose adjustment	
Caution, reduce dose in mild to moderate RI	Insulins (A10A), drugs for acid-related disorders (A02), quinolones (J01M), NSAIDs (M01A)
Reduce dose in severe RI	Penicillins (J01C), cephalosporins (J01D)
Start with small doses	Calcium channel blockers (C08), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C)
Caution	
Caution	Betablocking agents (C07A), ACE/angiotensin II antagonists (C09)
Caution, monitor serum conc.	Aminoglycosides (J01G)
Increased bleeding tendency	Antithrombotic agents (B01A)
Increased cerebral sensitivity	Opioids (N02A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C)
Avoid	
Avoid in mild to moderate RI	Thiazides (C03A), potassium-sparing agents (C03D, C03E)
Avoid in severe RI	Antithrombotic agents (B01A), bisphosphonates (M05B)

3.7 Drug interactions (DDIs)

Stockley uses a broad definition of interactions: *An interaction is defined to occur when the effects of one drug are changed by the presence of another drug, food, drink or some environmental chemical agent* (4). In computerised screening programmes for interactions, a more limited definition is applied, with the focus on drug-drug interactions.

The drug regimens were screened using of the internet-based Norwegian Drug Information Database (DRUID) (57). This program includes a generally accepted grading of drug interactions in relation to clinical significance (58).

In this programme DDIs are divided into four classes:

- Class A: Drug combination should always be avoided. Risk always outweighs benefit.

- Class B: Drug combination should usually be avoided. The actual combination should only be used when special precautions are taken. Use of other drug combinations should be considered, or if the combination is chosen, then the drug use should be monitored closely.

- Class C: The drugs can be combined, but action should be taken as necessary to reduce risk, for example changing timing of drug dose or the routes of administration.

- Class D: No action needed. Risk of adverse outcome appears to be small.

In addition to recording DDIs of different grades we noted whether the DDIs in classes A, B and C were new ones, that is to say, were connected to drug therapy started after admission to hospitals. Heightened awareness is required for new DDIs compared with interactions that have existed for a long time in the patient's drug regimen. We used the term DDI_{new} when the DDI was initiated by the addition of a new drug that could interact with a drug used at admission or with another new drug introduced at hospital.

In the bedside approach, only DDIs regarded as import and a clinical problem for the patient concerned were recorded as DRPs, regardless of type of interaction, i.e. type A, B, C or D. This implies, for example, that a type A DDI was only recorded as a DRP when the drug in question was assessed as being inappropriate for a specific patient. In the bedside approach other substances that could possibly cause interactions when used or taken in by the patient, e.g. tobacco, grapefruit juice and ethanol, were registered and assessed. We did not specifically ask for information on such substances, but if this information was contained in the medical record or communicated by the patients, possible interactions were assessed and, if considered to be a problem, included in the count of drug interactions (DDIs).

3.8 Quality assessment

The multidisciplinary meeting acted as a first body for quality assessment of the DRPs. In addition, an independent quality assessment team was appointed, consisting of a professor in pharmacotherapeutics, who is also a specialist in internal medicine, and two specialists in hospital pharmacy with long experience as clinical pharmacists. The DRPs of every sixth patient were randomly chosen for this quality assessment **(Figure 3.3)**. The team retrospectively assessed the clinical significance of the registered DRPs. Assignment of DRPs to categories of clinical significance was performed by the team (consensus method) after all three members had made their own evaluation. If the judgements differed, the case was discussed and consensus was reached.

The clinical significance was assigned to 4 categories: extremely important, major, moderate or minor:

1. Extremely important: DRPs requiring intervention in order to save life or prevent severe or irreversible detrimental effects. For example the need to discontinue oral hormonal contraceptives in a smoker admitted with possible pulmonary emboli.
2. Major clinical significance: DRPs requiring intervention in order to prevent a major to moderate or reversible detrimental effect or lack of accepted evidence-based therapy, for example the need for ACE inhibitors in patients suffering heart failure.
3. Moderate clinical significance: DRPs requiring intervention leading to moderate benefit for the patient, for example early switch to oral antibiotics.
4. Minor clinical significance: DRPs of little clinical importance for the patient, such as non-important time adjustments for dosages.

3.9 Ethics and approval

The study protocol and consent procedure was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services (NSD).

Data collection was approved by hospital directors, heads (chief physicians) of the involved departments and pharmacy directors. Data on each patient was collected using a standardised form and was coded by numbers. The code lists were kept at the hospitals.

3.10 Data handling and statistical analysis

The collected information was entered into a database constructed for the study. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system (59).

The data was analysed in SPSS 11.0 and 12.0 for Windows. Descriptive statistics are shown as means and frequencies with standard deviations or standard errors. P-values less than 0.05 ($p < 0.05$) were accepted as statistically significant.

In Paper I, a log-transformation was applied to ensure that the dependent variable followed an approximately normal distribution. The log-linear regression was carried out with the number of P-DRPs as the dependent variable and possible risk factors as independent variables, to explore the relationship between the occurrence of DRPs and different patient characteristics. In addition, the relationship between several of the most common DRPs and the risk factors was studied by means of a logistic regression.

In Paper II, Pearsons chi-square test was performed to examine associations between patient groups, gender and response. ANOVA tests were used to study differences between groups for the continuous variables of age, drugs used at admission, number of clinical/pharmacological risk factors and number of DRPs.

In Paper III, differences between patients with renal impairment, stages 3, 4 and 5 and patients with adequate function, stages 1 and 2, were tested by independent samples T-tests for continuous variables, and by chi-square tests for categorical variables. For each category of DRP, the Kruskal-Wallis test was used to test for differences in the mean number of DRPs per patient among patients with different stages of renal impairment, since these data showed strong deviations from the normal distribution.

In Paper IV, differences between patient groups with and without DDIs were tested. Independent samples T-tests were used for continuous variables, while chi-square tests were used for categorical variables.

4 Synopsis of the studies

4.1 Paper I:

Blix HS, Viktil KK, Reikvam Å, Moger TA, Hjemaas BJ, Pretsch P, Vraalsen TF, Walseth EK. **The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals.** Eur J Clin Pharmacol 2004;60(9):651-8.

Objective: To describe the frequency and types of drug-related problems (DRPs) in hospitalised patients and to identify risk factors for DRPs and drugs most frequently causing them.

Methods: From May to December 2002, 827 patients from 6 internal medicine and 2 rheumatology departments in 5 hospitals in Norway were included in this study. We recorded demographic data, drugs used, relevant medical history, laboratory data and clinical/pharmacological risk factors i.e. reduced renal function, reduced liver function, heart failure, diabetes, compliance problems, drugs with a narrow therapeutic index and drug allergy. DRPs were documented after reviewing medical records and participation in multidisciplinary team discussions. An independent quality assessment team retrospectively assessed the DRPs in a randomly selected number of the study population.

Results: 81% of the patients had DRPs and an average of 2.1 clinically relevant DRPs was recorded per patient. The DRPs most frequently recorded were dose-related problems (35.1% of the patients) followed by need for laboratory tests (21.6%), non-optimal drugs (21.4%), need for additional drugs (19.7%), unnecessary drugs (16.7%) and medical chart errors (16.3%). The patients used an average of 4.6 drugs at admission. A multivariate analysis showed that the number of drugs at admission and the number of clinical/pharmacological risk factors were both independent risk factors for the occurrence of DRPs, whereas age and

gender were not. The drugs most frequently causing a DRP were warfarin, digitoxin and prednisolone, with calculated risk ratios 0.48, 0.42 and 0.26, respectively. The drug groups causing most DRPs were B01A-antithrombotic agents, M01A-NSAIDs, N02A-opioids and C09A-ACE inhibitors with risk ratios of 0.22, 0.49, 0.21 and 0.35 respectively.
Conclusions: The majority of hospitalised patients in our study had drug-related problems. The number of drugs used, and the number of clinical/pharmacological risk factors, significantly and independently influenced the risk for DRPs. Procedures for identification of, and intervention on actual and potential DRPs, along with awareness of drugs carrying a high risk for DRPs, are important elements of drug therapy and may contribute to diminishing drug related morbidity and mortality.

4.2 Paper II:

Blix HS, Viktil KK, Moger TA, Reikvam Å.

Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. Pharm World Sci 2006;28(3):152-8.

Objective: To investigate pharmacist contribution in the therapeutic hospital team by studying drug-related problems (DRPs), pharmacist therapy advice and consequences of the advice.
Methods: From May to December 2002, 827 patients in 5 Norwegian hospitals were included in the study. Demographic data, drugs used, relevant medical history, laboratory data and clinical/pharmacological risk factors were recorded prospectively at the wards.
Main outcome measure: DRPs, patients characteristics, pharmacist advice to physicians, nurses or patients, response to the pharmacist advice, and reasons (stated by the pharmacist)

for not discussing an identified DRP, were reported. An independent quality assessment team retrospectively assessed the DRPs for a randomly selected number of the study population.
Results: On average 2.6 DRPs per patient were found. A total of 2128 DRPs were registered and of these 1583 (74%) DRPs were brought up for discussion. Physician immediate acceptance rates varied from 80% (for extremely important clinically significant DRPs) to 50% (for DRPs of minor clinical significance). High age, use of many drugs at admission, existence of many DRPs and many clinical/pharmacological risk factors for DRPs were associated with low immediate acceptance rate. Type of DRP influenced how the DRP was discussed; adverse drug reaction (ADR) and unnecessary drug were discussed with physicians while e.g. medical chart error and need for patient education were discussed with nurses/patients. Reasons for not discussing DRPs in the team were: not given priority (37%), no longer relevant (31%) and others (31%). DRPs of minor clinical significance were most often excluded from discussion (37%) as opposed to 14% and 22% of those of moderate and major clinical significance.
Conclusions: The majority of patients had one or more DRPs. The problems identified as DRPs by the pharmacists were accepted as such by the physicians and to a high degree acted upon. Both clinical significance of the DRP and patient characteristics influenced physician immediate acceptance rate. Some DRPs could be solved by direct contact with nurses or the patients. Awareness of DRPs increases through participation of pharmacists in the multidisciplinary therapeutic hospital team.

4.3 Paper III:

Blix HS, Viktil KK, Moger TA, Reikvam A.

Use of renal risk drugs in hospitalized patients with impaired renal function – an underestimated problem? Nephrol Dial Transplant. 2006;21(11):3164-71.

Background: Inappropriate use of drugs in patients with renal impairment (RI) may be harmful and have deleterious effects. We aimed to investigate the use of renal risk drugs in such patients in general hospitals and to analyse the relationship to demographic factors, risk factors and occurrence of drug-related problems (DRPs).

Methods: Patients admitted to departments of internal medicine and rheumatology in 5 general hospitals were included. We recorded demographic data, drugs used, drugs described to be a risk in RI (renal risk drugs), relevant medical history, laboratory data and clinical/pharmacological risk factors. We used levels of glomerular filtration rates (GFR), calculated by the Modification of Diet in Renal Disease (MDRD) formula to classify patients into five stages of renal function. DRPs were recorded and assessed in multidisciplinary hospital team discussions.

Results: Of the 808 included patients: 293 (36%) had normal renal function (stage 1), 314 (39%) had mild RI (stage 2), 160 (20%) had moderate RI (stage 3), 35 (4%) had severe RI (stage 4) and 6 (0.7%) had kidney failure (stage 5). Mean number of drugs used per patient in patients with RI (stages 3, 4 and 5) and patients evaluated to have adequate renal function relative to drug therapy (stages 1 and 2): on admission 6.2 vs. 4.1; started in hospital 4.3 vs. 3.9; total number of renal risk drugs 6.1 vs. 4.5. All but six patients with RI stages 3, 4 and 5 used two or more renal risk drugs. 124 (62%) of the patients with RI stage 3, 4 and 5 had DRPs linked to the renal risk drugs, and 26% of the renal risk drugs were associated with

DRPs. The most common drug classes associated with DRPs were antibacterials, antithrombotic agents, ACE inhibitors, opioids and NSAIDs.

Conclusions: Among patients admitted to general hospitals, a considerable proportion had renal impairment. In patients with reduced renal function, renal risk drugs were widely used and often in combination. DRPs were frequently associated with the use of renal risk drugs.

4.4 Paper IV:

Blix HS, Viktil KK, Moger TA, Reikvam A.

Comparison of two methods for identification of drug interactions: computerised screening versus bedside recording. Submitted.

Objective: To compare two methods for identification of drug interactions (DDIs) - computerised screening and prospective bedside recording - with regard to capability of identifying DDIs.

Methods: Patient characteristics were recorded for patients admitted to five hospitals. By bedside evaluation drug-related problems, including DDIs, were prospectively recorded by pharmacists and evaluated in multidisciplinary teams. A computer screening programme was used to identify DDIs retrospectively - dividing DDIs into four classes: A, avoid; B, avoid/take precautions; C, take precautions; D, no action needed.

Main outcome measure: Proportion of patients with DDIs; number and types of DDIs.

Results: Among 827 patients computer screening found DDIs in 544 patients (66%); 351 had DDIs introduced in hospital. The 1513 computer identified DDIs had the following distribution: type A, 78; type B, 915; type C, 38; type D, 482. By bedside evaluation, DDIs

were found in 73 patients (9%), with a total of 99 DDIs. The proportions of computer recorded DDIs which were also identified bedside were: 5%, 8%, 8%, 2% of DDIs type A, B, C, D, respectively. In 10 patients, DDIs not registered by computer screening were identified bedside. By computer screening, the drugs most frequently involved in DDIs were acetylsalicylic acid, warfarin, furosemide and digitoxin and by bedside evaluation warfarin, simvastatin, theophylline and carbamazepine.

Conclusions: Despite active prospective bedside search for DDIs, this approach identified only a small proportion - less than one in ten - of the DDIs recorded by computer screening. This also pertained to DDIs reported by the computer screening to be hazardous. Computer screening overestimates considerably when the objective is to identify clinically relevant DDIs.

5 General discussion

The results of the separate papers (Papers I-IV) constituting this thesis have been considered in the discussion section of each of the papers. Thus only the most important findings are discussed here.

5.1 Main results

- The majority of hospitalised patients had DRPs
- In logistic regression analysis both the number of drugs at admission and number of clinical/pharmacological risk factors were independent risk factors for occurrence of DRPs, but age and gender were not
- The observed *drug risk ratios* for the various drugs exhibited a wide range of variation
- DRPs identified by pharmacists were largely accepted as such by the physicians and to a high degree acted upon
- The physicians' rate of immediate acceptance was influenced by the clinical significance of the DRP and by special patient characteristics
- The clinical significance of the DRP influenced whether or not it would be discussed by the multidisciplinary team
- Some DRPs could be solved directly through contact with nurses or the patients themselves
- A sizeable proportion of hospitalised patients had renal impairment; renal risk drugs were widely used in these patients and often in combination
- DRPs were frequently associated with the use of renal risk drugs
- A prospective bedside approach identified only a small proportion – less than one in ten – of the DDIs reported by computer screening

- Computer screening highly overestimates DDIs and is of limited value for assessing DDIs

5.2 Discussion of main findings

5.2.1 DRPs (Aim I)

Our finding of a high frequency of DRPs at clinical departments – over four-fifths of the patients had one or more DRPs – highlights the benefit of establishing a multidisciplinary team with the task of making a holistic assessment of the drug therapy. Patients admitted to hospital need special attention as regards drug therapy. Often they are severely ill and will be prescribed many potent drugs during the acute phase. Exacerbation of the disease or contraction of infection may temporarily influence drug pharmacokinetics and pharmacology. Such situations present a huge challenge to hospital physicians, who often need to take rapid decisions that might also influence the effects of the patient's stable long-term drug regimens. In the medical hierarchy the hospitals are specialised in acute care, and the segregation into departments with high clinical expertise on specific diseases will provide good and focused treatment for the conditions that caused admission to hospital. However, the specialisation may imply less focus and expertise as regards the treatment of the patients' concomitant disorders.

The large amount of DRPs identified in our study reflects the chosen definition of DRPs, which includes potential as well as actual DRPs. It has been debated whether a potential DRP that does not necessarily become a real concrete problem, should be included in the term DRP (60-62). We would argue that a potential problem should be regarded as a DRP because – if not dealt with properly – it will frequently cause negative outcomes. Many

studies have shown that a large proportion of DRPs causing hospital admissions are preventable (15;16;18;22;63-66), which emphasises the need to take potential DRPs into consideration when evaluating drug regimens. The definition of drug-related problems (DRPs) has been widely discussed but, as yet, international agreement has not been achieved (53;60-62).

The area "DRPs" overlaps with the area of "Medical Errors". Both these areas are of significant concern (67). The extended concept of Medical Errors has been awarded massive attention in the United States since 1999, when the Institute of Medicine published their report: "To Err is Human: Building a safer Health system" (7). This issue has received attention in Norway as well, and strategies have been developed to reduce the problem of errors in medication (68). However, these strategies refer mainly to administrative management and quality assurance. A DRP as such is not always a consequence of error, it may rather be a consequence of changes in pharmacology, pharmacokinetics, severity of the disease, or adjacent events that are difficult to foresee.

In the literature, considerable differences in DRP frequency have been reported (19;69-74). The lack of standardised methods for identifying prevalence of DRPs restricts the possibility to compare therapeutic traditions across settings, hospitals and countries. Much of this controversy can be explained by differences in the definition and operationalisation of the term. One element of the discussion concerns whether the definition should include potential DRPs. It has also been debated what categories of DRPs should be included. Clusters of problems have been called "drug-related problems" (53), "medicine-related problems" (75;76), "medication-related problems" (71;77), "inappropriate drugs" (78) "negative clinical outcome" (62), "suboptimal prescribing" (79) and so on. To be able to make relevant comparisons there has to be methodological similarity. At the present time different operational classifications of DRPs are used (5;53;60;80;81). The classifications are not

consistent and the variation can be confusing. International agreement on the definition of the term as well as recommendations for easy, practical and reliable operationalisation of the term, is urgently needed. Only after this has been achieved can we get a clear picture of what we actually are discussing.

The area of DRPs is important for society in terms of health costs and quality of care. The lack of standardised operational classification tools makes it difficult, not only for researchers in the field, but also for quality assurance that could have made use of a unified DRP classification system for clinical documentation, as well as for comparisons, for example, between different practices, wards or hospitals. Tools aimed at improving the quality of prescribing, such as audits and retrospective feedback on practice, have been frequently utilised in quality assurance (82-84). These tools have been shown to have some effectiveness in improving professional practice (26). For the individual clinician, feedback on his/her own practice is often more educational and encouraging than for example comparisons across borders, owing to differences in therapeutic traditions, health care systems and health culture. Quantification of DRPs might possibly serve as a quality indicator for drug use and accordingly be used in quality procedures, in hospitals, general practice and pharmacies.

International agreement on the DRP notion seems to take time, so in the meantime a national standard would be advantageous. In Norway, the present study is the first to look into the extended area of DRPs in hospitals. Together with a research group in Bergen, who have carried out a study on DRPs in nursing homes and used a different tool of classification (85), we have recently developed a common tool for identification of DRPs. This tool is intended to be used by professionals in the field and applied in general practice, pharmacies, nursing homes and hospitals. It can be used to identify DRPs within the patients' drug regimens and in summaries depicting the practitioners' work on DRPs, or it can be used in research. The system is simple in form, but can easily be transformed into a more complicated instrument

for research (**Appendix II**). However, if this tool is to be used as an indicator of quality, it is necessary to undertake a validation procedure and to test out whether it can indeed be used as such (86;87).

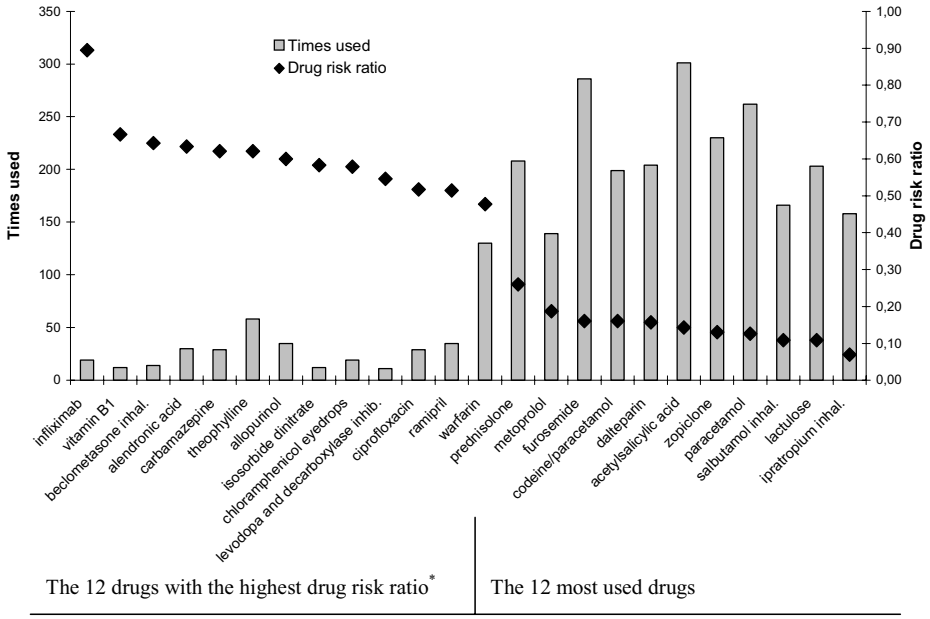
5.2.2 Risk factors for DRPs (Aim II)

The identification of risk factors for DRPs may be helpful in finding patients at risk. These patients can then be singled out for special attention, with the hope of avoiding overt DRPs. We found that an increased number of clinical/pharmacological risk factors significantly heightened the risk of occurrence of DRPs. The clinical/pharmacological risk factors were identified from a predetermined list of acknowledged factors described in the literature. It may be difficult to use the cluster of clinical/pharmacological risk factors in connection with individual patients, since this composition of factors is heterogeneous and relates to diseases, drugs and behaviour. In clinical practice it is often easier to deal with one risk factor, for example renal impairment, at a time. However, in reports and surveys in the field of health administration, it may be practical to use the mean number of clinical/pharmacological risk factors per patient in a particular department as an indicator of the risk of DRPs. This information can be used to identify high-risk departments in need of clinical pharmacist services.

We found a strong relationship between an increasing number of drugs used and increasing number of DRPs, which is not surprising. However, this risk factor for DRPs is difficult to utilise in clinical practice. This issue was highlighted by the results from another study in this project (88) where it was concluded that setting a strict cut-off and defining polypharmacy as the use of more than five drugs, for example, offers no advantage.

It is important to identify drugs that are prone to create problems. We introduced the *drug risk ratio* to quantify this tendency among the various drugs. A more comprehensive drug list than the one presented in Paper I is shown in **Figure 5.1**. It is necessary to be aware of the drugs with the highest *drug risk ratio* since these are those that most frequently expose the patient to risk when taking these drugs. On the other hand, it is also necessary to be aware of frequently used drugs with a lower *drug risk ratio*. Because these drugs are commonly used health workers may consider them safe. However, a *drug risk ratio* of 0.26, which was the ratio found for prednisolone, means that, in fact, a DRP may occur in one fourth of the times the drug is used.

Figure 5.1 *Times used and drug risk ratio for the 12 most utilised drugs (right) and for the 12 drugs with highest drug risk ratio (left).*



*Selected among the drugs used more than 10 times

5.2.3 Clinical pharmacists (Aim III)

Handling of identified DRPs is not a straightforward procedure. In a British study, 45% of the participating GPs felt they did not have the adequate skills to solve medicine-related problems (89). DRPs are probably handled most successfully by multidisciplinary teams. In the end, permanent drug changes should be implemented in collaboration and concordance with the patient. This is the ideal situation that probably would give the best results. In the setting of acute hospital medicine it is difficult for the patient to achieve adequate understanding of complicated therapies. Therefore it is sensible that professional discussions on the optimal handling of DRPs – and associated drug reviews – be held within the hospital team, after which the therapeutic options can be presented to the patient.

Historically, physicians have been wholly responsible for the patient's therapeutic management. They still make the final decision but nowadays pharmacists are becoming increasingly involved in the management of the patients' drug regimens by providing comprehensive medication reviews, educational efforts directed at patients and health personnel and by proactive participation in multidisciplinary teams. Clinical pharmacists are supposed to possess an in-depth knowledge of medications and also have a fundamental understanding of biomedical, pharmaceutical and clinical sciences. The inclusion of clinical pharmacists into the hospital health care team has been shown to result in fewer ADRs , fewer medication errors, improved drug adherence, better patient knowledge of drugs, reduced hospital stay and lower costs (41;90).

In Norway, the first clinical pharmacy services were established as a routine in 1996. The services observed in the present study (2002) were provided mainly by pioneers in the field. The study was undertaken in departments with established clinical pharmacy practices, organised with pharmacists as parts of the multidisciplinary team. The clinical pharmacists

had the specific task of searching for DRPs and solutions were found in collaboration with other health care workers. We found that most of the identified DRPs were discussed in the team, indicating that the pharmacists are active partners in the multidisciplinary discussions. This way of handling DRPs is labour intensive, requiring a high work load by clinical pharmacists. However, it is probably the most effective approach to the problem, since continuous high intensity monitoring ensured that many DRPs that may otherwise have been overlooked were discovered. This view is supported by reports from other researchers (91;92). The multidisciplinary team approach implies stronger focus on questions of drug therapy at the meetings. This appears to be time consuming, but since the questions are often the same in other similar cases and the solutions often transferable, the team meetings could have an educational effect, with continuous updating of drug therapy in clinical practice.

Nowadays, costs are very much in focus in the hospital sector of health care. The presumed outcome of reducing DRPs – less drug-related morbidity – generates savings to society as a whole. The added value will be avoidance of hospital admission, a shorter stay in hospital, more beneficial use of drugs and more optimal use of other health care services. However, since the savings are often not directly connected to the specific hospital involved it may be difficult to convince hospital administrators that investing money in prevention of DRPs is worthwhile in the long run, since their primary task is to look after their own budget. However, by applying a broad perspective, and considering society as a whole, it appears that investing money in preventing DRPs is worthwhile and cost effective in the long term. Studies, although not in Europe, have shown that the costs of incorporating clinical pharmacists into multidisciplinary hospital teams give a net hospital cost benefit (41;42;93-98). These findings provide circumstantial evidence that the introduction of clinical pharmacy practices in Norwegian health care may well contribute to savings in the public health care budget.

5.2.4 Priorities and advice (Aim IV)

An important issue rarely studied is how pharmacists deal with DRPs. Although not surprising, our finding that DRPs of minor clinical significance are more often omitted from discussions than are DRPs of greater significance has not been reported before. Furthermore, to our knowledge, our study is the first to investigate the reasons for pharmacists not intervening in the case of an identified DRP. The main reason was the setting of priorities, an important factor for hospital efficiency. Ideally, all DRPs should be addressed, but in clinical practice it is necessary to be pragmatic, to focus first on major issues. In our study, the grouping of reasons for the pharmacists not discussing a DRP – *no priority, not relevant, others* – was somewhat inaccurate. Nevertheless the data demonstrate how the pharmacists reason and carry out their work on DRPs.

Another issue related to priority concerns patient characteristics. Why was it that patients with several DRPs, who exhibited many potential risk factors for DRPs, and who were taking many drugs were less likely to have all their DRPs brought up for discussion by the pharmacist than other patients were? Was this because the pharmacists took the view that "this is too much to deal with"? We have not found any other study looking into how clinical pharmacists reason when encountering DRPs. In any case, it is important to tackle inequalities in delivery of service, and further studies are needed to provide a better understanding of this issue.

Advice from pharmacists on the multidisciplinary team was well received by the physicians. The majority of the DRPs brought up by the pharmacist were acted upon. The rates of acceptance were in line with the results from other studies (99-104). Could it be that, without proposals from the clinical pharmacist, the physicians would have taken the same decisions regarding drug therapy? If so, the contribution of clinical pharmacists is

overestimated. However, given the magnitude of DRPs identified, the nature of the interventions, and the wide variation of addressed drugs, it is likely that the handling of DRPs reflects the pharmacists' focus on drugs and that the presence of pharmacists on the team creates a general alertness to drug issues among all members of the team.

Worldwide, there is a call for the pharmacist profession to help improve drug safety and outcomes (46;67;105). Pharmacist workforce shortage is a problem in Norway, but the clinical pharmacy discipline, which is a branch of the pharmacy profession, is popular among young pharmacists. In Norway today, it is a drawback that the undergraduate pharmacy curriculum does not focus on clinical pharmacy. However, plans have been put forward to start a new Masters programme in clinical pharmacy at the School of Pharmacy, University of Oslo. In line with this proposal, the University should make efforts to comply with the grass-root demand to develop scientific competence in this area.

5.2.5 Drug use in patients with renal impairment (Aim V)

Renal risk drugs

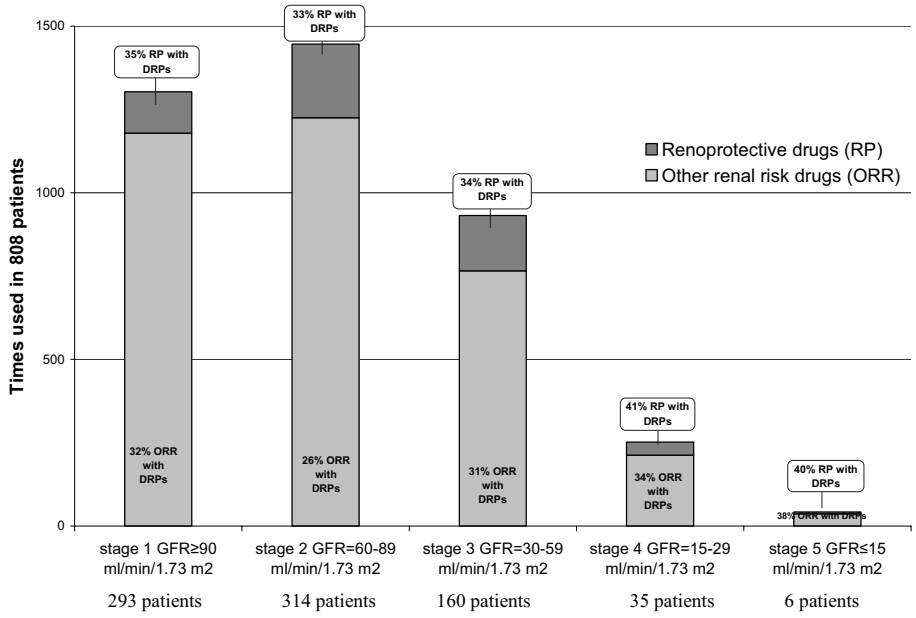
It is possible that many patients with moderate to minor renal impairment are treated inappropriately. Mild renal impairment is often overlooked, and the result may be unfortunate drug use and drug dosages. This could exacerbate the renal impairment and lead to ADRs. For many drugs renal elimination is important. This is both recognised and addressed in the Summary of Product Characteristics, in drug catalogues and in separate lists of drugs with rules for caution in cases of renal impairment. However, as our study has shown, when it comes to clinical practice, this information seems to be overlooked or ignored. Certainly, in some cases, the use of renal risk drugs could be defended, and they might have been used

deliberately. For example, some of the drugs would have been prescribed to prevent cardiovascular events and in these situations the risk of worsening renal function is a calculated one. However, some drug use could also be due to ignorance – it is easy to forget rules of caution when it comes to common drugs that produce few adverse events. When a patient presents with mild to moderate renal impairment, various questions concerning drug therapy should be raised: Which drugs and which doses are optimal? Should the drug be continued, or should one switch to another drug? In hospitals, where patients stay for only a short time, a wise solution would probably be to continue the current treatment unless the renal function becomes severely deteriorated. On the other hand, it is easier to elaborate on a patient's renal function in hospital, and recommendations for well-founded drug changes could be included in the discharge report.

It has been shown that some drugs associated with rules of caution also are renoprotective in the long term (106-109). These drugs – ACE inhibitors, angiotensin II antagonists, calcium channel blockers and the statins – were frequently used by the patients in our study and were often involved in DRPs (**Figure 5.2**). These renoprotective drugs are challenging to handle, since the balance between efficacy and adverse effects is a fine one.

It could also well be that other renal risk drugs (i.e. other than those mentioned above) may have a positive or a negative long-term impact on renal function. This can only be clarified by future epidemiological studies in patients with renal impairment. Furthermore, little is known about the effects of a combination of renal risk drugs – one would assume that two renal risk drugs would have synergistic or additive negative effects on the kidney. This lack of knowledge is a problem for clinicians treating patients with minor to moderate renal impairment. More research in this area is needed to enable reliable advice on drug use in these patients.

Figure 5.2 *Use of renal risk drugs divided into a) those that also are renoprotective and b) other renal risk drugs. The figure also shows the relationship to occurrence of DRPs for the two groups.*



Methodological considerations

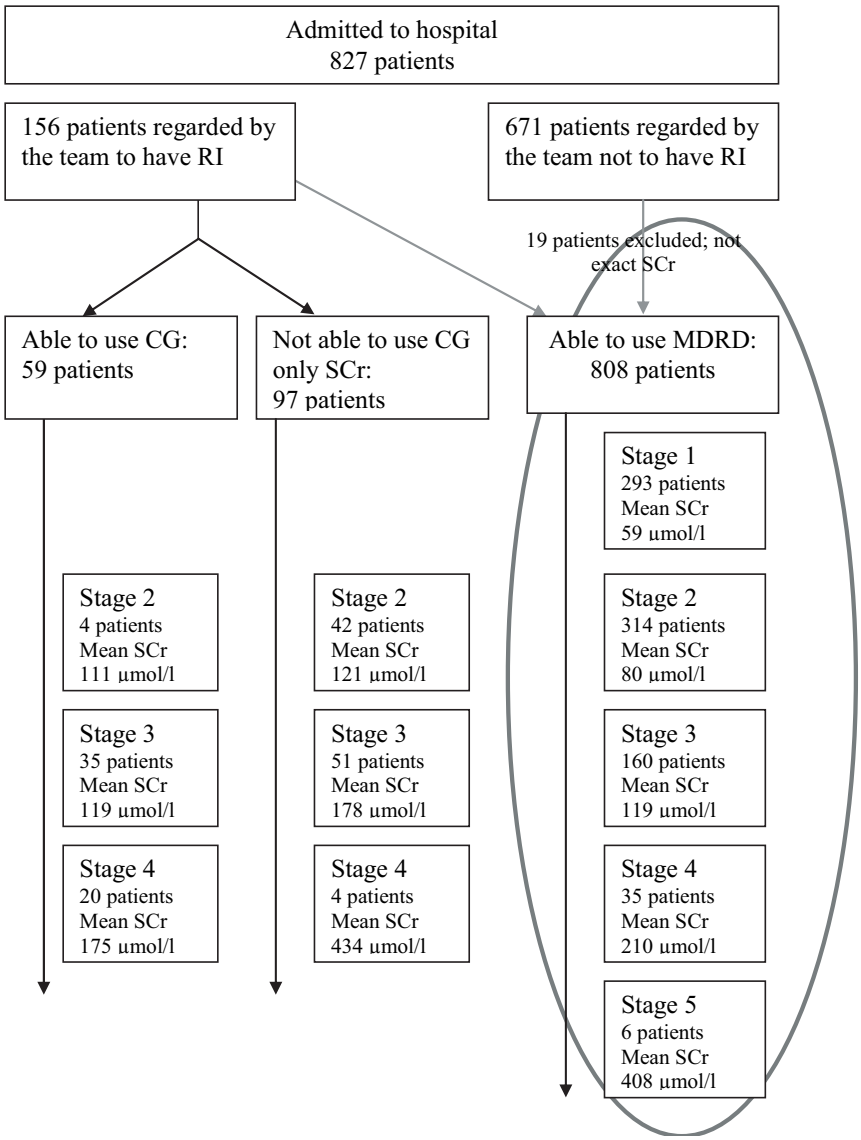
The Cockcroft-Gault equation is regarded to be a rough, but good bedside estimate of renal status in the elderly. Since many of our patients were old this seemed to be a good option, and in the initial analysis GFR was estimated by this method for those patients where information on weight was available. During the study the multidisciplinary health team evaluated whether the patients had significant clinical reduction of renal function, defined as GFR less than 50 ml/min (see Methods 3.3). This evaluation was based on either the calculation of renal function from the Cockcroft-Gault formula or, on a pragmatic clinical approach − grading only on the basis of SCr levels − for those patients whose weight was not known. Using SCr only is a method commonly used by physicians, and when the SCr is obviously raised, this situation creates awareness with regard to drug handling. However, an estimation

based on SCr alone is not unproblematic, since SCr is not a good indicator in very old patients. Progressive reduction of muscle mass with ageing reduces the production of creatinine, and this may parallel a real decrease in renal function. The result is that the SCr-level remains unchanged and a renal impairment will be masked (110;111). The initial analyses revealed a marked inconsistency between the groups analysed by these two ways; Cockcroft-Gault and SCr alone (data not given). The data indicated that some patients in the SCr group might have had more severe renal impairment than estimated. Struggling with this selection bias we realised that the MDRD method, which has become increasingly used in recent years, was a good and reliable method for estimating GFR. Therefore, retrospectively we decided to use that method on the whole patient population.

The GFR grading achieved by the two methods (the initial Cockcroft-Gault/SCr and the retrospective MDRD) differed to some degree, but the difference was not pronounced. There was a trend towards more severe grading when applying the MDRD formula (**Figure 5.3**). In general, however, the findings with regard to drug use were the same whether the analyses were made with renal impairment diagnosed on the basis of the MDRD formula or by the other method combining the Cockcroft-Gault equation with clinical evaluation of SCr.

Figure 5.3 *Number of patients and mean SCr values in patients in various stages of RI*, applying different methods. Three ways of grading renal impairment (RI) are shown: a) calculation of GFR by the Cockcroft-Gault equation (CG), b) estimation of GFR by clinical evaluation of SCr, c) calculation of GFR by the MDRD formula. (Only the MDRD formula was used for the calculations in Paper III).*

* see Table 3.2



5.2.6 Drug interactions (Aim VI)

Drug interactions (DDIs) may be responsible for a substantial number of hospital admissions (18;112-114). In hospitals many new drugs are added and many new DDIs are introduced (115). The presence of drug interactions in a patient's drug regimen is common but the number of clinically serious DDIs is reported to be low (116-119). This agrees with our findings.

In many countries sophisticated computer software is available for screening medication profiles with the objective of detecting DDIs. These databases are adapted to the national market, that is to say, they include only drugs with marketing authorisation in the country concerned. In hospital it is not uncommon to use non-licensed products. Such drugs are either imported from other countries or prepared by special service production; they are not included in the database constructed to detect drug interactions. Of course, global drug interaction screening programmes (120) could have been used, but in clinical practice prescribers are most familiar with the brand-name, not the generic name of the drug. Hence computer software adapted to the national market is preferable, since this will be the most user-friendly tool.

Although DDIs can be discovered by reviewing the patients' drug regimen by means of computer screening programmes, these programmes come up with a large proportion of theoretical alerts that may be of only minor clinical significance. These DDI alerts are not necessarily meaningless or a waste of time, considering that DDIs constitute an important cause of ADRs, but it is necessary to have health care workers who have the skill to understand and combine clinical and pharmaceutical information in order to interpret the outcome of the screening. Properly used, a computer screening programme used could reduce the magnitude of severe interactions (121). Such a screening programme should never be used

alone, however, since computer programmes are not flexible in the sense of being able to evaluate clinical information regarding health status and individual patient characteristics. Our study demonstrated this point and showed that many DDIs signalled by computer screening to be severe were in fact introduced intentionally and probably to the benefit of the patients.

Important interactions may also arise as a result of the use of complementary and alternative medicines and normally these interactions are not included in computerised surveillance programmes. Herbal medicines are widely used (122), and a recent study found that almost one-third of current users of herbal medicines were at risk of a herb-drug interaction (123). Neither do the computer screening programmes include drug interactions linked to alcohol or smoking. Thus, for example, if precautions are not taken, patients using theophylline may experience severe ADRs if they stop smoking, caused by an elevated level of serum theophylline. By contrast, clinical evaluation could have picked up that a stable smoking-drug interaction was going to be disturbed. Owing to the lack of comprehensive summaries, interactions other than drug-drug interactions are left to be judged by the prescriber, an often difficult and challenging task.

5.3 Internal and external validity

This section addresses the internal and external validity of the study. Associations found in the study must be a result of causation, chance, bias or confounding (124). There are two kinds of errors that could influence the conclusions, random errors (chance) and systematic errors (bias). Precision (lack of random error) can be improved by enlarging the study sample or by modifying the study design. Our study was carried out in clinical practice and the design had to be adapted to daily hospital routines. This strengthens the external validity of the study. The inclusion of about 800 patients was estimated to be abundant to make in-depth analyses

and draw valid conclusions – for the whole material and for a number of subgroups. On the basis of the above, we also estimated that it would be sufficient to let every 6th patient undergo evaluation by the quality assessment team – and let every 4th patient be interviewed by clinical pharmacists.

5.3.1 Internal validity

Various biases that could reduce the validity of results are discussed. The main types of systematic errors are selection bias, information bias and confounding (124).

Selection bias

Selection bias results from the way patients are selected into the study, the problem being that the patients might not be representative of the population we want to study (124). All patients admitted to the participating departments were eligible for inclusion and selection bias should thus have been avoided. In order to prevent preferential selection of patients to the quality assessment, we used random selection; every 6th patient recruited to the study would be assessed by the quality team. This implies that our results are presumed to be representative for patients admitted to departments in Norwegian hospitals.

In Paper III a crucial objective was to grade renal function. The original data recording form had a column for SCr values. The SCr values were to be used to estimate GFR since our primary aim was to look at reduced renal function as a risk factor for DRPs. However, the data collectors sometimes omitted to note the exact SCr value if the patient was undoubtedly considered to have normal kidney function on the basis of laboratory tests and medical history. After the data collection, we reconsidered the method of calculating renal function and decided to use the MDRD formula instead of the Cockroft-Gault formula. This was

because the former method of evaluation has been increasingly recommended by nephrologists in recent years. By using the MDRD method we were able to calculate GFR for the majority of the enrolled patients, but 19 patients had to be excluded from the analysis owing to lack of exact SCr values. These 19 patients were distributed between all hospitals and all departments, indicating that selection bias would not be induced by this omission. Thus it is likely that the results as regards both the occurrence of renal impairment and drug use are valid for other similar departments.

Information bias

Information bias results from the way information is obtained (124). Information on the patients' drug regimens was collected from medical charts, medical records and data gathered on the physicians' rounds, and sometimes also after pharmacists had interviewed the patients. In our study, the patients' drug profiles at admission, that is to say, the drugs they had been using at home, were ascertained through normal hospital admission procedure. The patients were interviewed by physicians in the admission unit and the information obtained was recorded by hand on the medicine chart. Several studies have shown that this way of acquiring information on drugs can be imperfect (125-129). Often, chronic medication not detected at admission but recognised later by ward staff is added to the medicine chart. Since the medication chart was one of the sources of information for the data collectors, a pertinent question is whether the recognised drug list was correct. In a subproject of our study, pharmacist interviews with patients on their medication (130) revealed additional DRPs, some of which related to drug use not identified at admission. Only 96 of the 827 patients were interviewed, however. The interviewed patients were randomly chosen for interview, which implies that, in the case of the patients who were not interviewed, some of the chronic medication being used may have been missed and, as a consequence, also some of the DRPs.

However, this bias probably did not influence the number of patients having DRPs, since the majority of patients (i.e. 81% of the patients) had already been identified as having DRPs.

The procedure whereby DRPs are allocated to specific categories also entails risk of misclassification. The allocation was made by the data collector. It is possible that the evaluation of a DRP by one data collector may differ from that made by another, implying that the assignment of the DRP to the different categories may not have been done uniformly. This can be demonstrated by an example: *A patient is admitted to hospital with chronic obstructive pulmonary disease (COPD). He uses prednisolone tablets daily. Prednisolone was prescribed half a year ago in connection with a previous hospital stay after which the patient was discharged with a one week treatment with prednisolone. Despite the intention of a limited period of treatment, prednisolone was still being used.* This DRP could be allocated to either "*unnecessary drug"* or to "*no further need"*. To avoid this type of misclassification the data collectors discussed possible wrong classifications before starting the study itself. Although some degree of misclassification might still have taken place, this should not have occurred for the DRP category "*drug interaction*", because all allocations to that category were based on explicit lists of interactions. Moreover, for the majority of DRPs, misclassification was not a real problem and, hence, this type of information bias is unlikely to have influenced the main results of the study.

The degree to which pharmacists identify and bring up DRPs for discussion will depend on their experience in this connection (103). All the clinical pharmacists in our study were experienced and their clinical pharmacy service was a routine function. A new service introduced as a part of a research project and using inexperienced data collectors might have resulted in different intervention and response outcomes. The strength of using routine services for the research on pharmacist interventions implies that the results reflect daily practice and are little influenced by collection bias.

Another strong point of our study was that it involved only few data collectors, all of whom had participated in the development of the study protocol and testing of the data collection forms. By choosing this design, we ensured that the data would be comparable and reliable.

Confounding

A confounding factor is a distortion of an exposure-outcome association brought about by the association of another factor with both outcome and exposure. The confounder needs to be a risk factor for the outcome, associated with the exposure under study, and must not be affected by the exposure or by disease (124). Confounding may be prevented by including randomisation in the study design. We used random selection to two subsets of patients for study, first to select patients for quality assessment and second to select patients for pharmacist interview (130). In this way we tried to avoid confounding.

Confounding can also be corrected for in the analysis. In our study we addressed confounding by using multivariate analyses when examining the occurrence of DRPs. In Paper I logistic regression was carried out to find the relationship between DRPs and risk factors. The selection of risk factors included were the ones most often mentioned in the literature giving rise to heightened risk of DRPs. Socio-demographic factors like education, domicile and civil status are other factors that might influence level of risk. Such factors have been reported to have an impact on morbidity and mortality (131;132). However, no data were collected on these factors, which therefore could not be evaluated.

5.3.2 External validity

A study is externally valid if it can produce valid results beyond the subjects in the study. Our study was conducted in 2002 in eight departments distributed between five hospitals in Norway. Since it is a multicentre study undertaken in different geographical areas, the results could probably be translated to other departments of internal medicine and rheumatology in Norway and, furthermore, to a large extent to hospitals in other countries.

5.4 Implications and further research

The results from papers I-IV in this thesis raise a number of pharmacotherapeutic issues in relation to drug use in hospital. Particular focus should be placed on the transition to primary care. At the hospital new and potent drugs are often added to the drug regimens and, in addition, other drugs withdrawn. Consequently, it is of major and practical interest what happens after the patients are discharged from hospital. This is an area of concern. Seamless care – safe patient transition from hospital to home, implying better communication between hospital and primary care – has been focused on and demanded (133). So far, research on this issue has dealt mainly with the avoidance of medical errors and compliance. The follow-up on DRPs should also be addressed.

6 Conclusions

We have demonstrated that the majority of patients admitted to hospitals have DRPs, usually each patient has several. Furthermore, we have shown that clinical pharmacists function as catalysts in the multidisciplinary team by initiating the identification and solving of DRPs.

We have also pointed out that explicit lists of drug interactions and of drugs that should be used with caution in patients with renal impairment are long and comprise many common drugs that seldom create problems. Furthermore, these lists are not precise enough as regards clinical significance to be used as a routine in clinical practice.

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